REMARKS

Claims 26-37 were pending claims. Claims 28, 30, 39-30 and 39-45 have been canceled. Claims 26, 27 and 29 are amended. No new matter is added. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Applicants respectfully request reconsideration of the application in view of the remarks made herein. Rejections of canceled claims are made moot and are not further considered.

Claim 29 has been rewritten in independent form, incorporating all of the limitations of base claim 26.

Claims 26-37 have been rejected under 35 U.S.C. 112, first and second paragraph. Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112, first paragraph. The claims have been amended to clarify the nature of the target sequence, which is an intracellular molecule present in the cell expressing the candidate bioactive peptide, to which the bioactive peptide binds.

The claims recite the use of a presentation structure encoded by nucleic acid sequences comprising a molecular library. As discussed in the specification, at page 6, line 20 ff, by "presentation structure" or grammatical equivalents herein is meant a sequence, which, when fused to candidate bioactive agents, causes the candidate agents to assume a conformationally restricted form. Proteins interact with each other largely through conformationally constrained domains. Although small peptides with freely rotating amino and carboxyl termini can have potent functions as is known in the art, the conversion of such peptide structures into pharmacologic agents is difficult due to the inability to predict side-chain positions for peptidomimetic synthesis. Therefore the presentation of peptides in conformationally constrained structures will benefit both the later generation of pharmaceuticals and will also likely lead to higher affinity interactions of the peptide with the target protein. This fact has been recognized in the combinatorial library generation systems using biologically generated short peptides in bacterial phage systems. A number of workers have constructed small domain molecules in which one might present randomized peptide structures. Synthetic presentation structures, i.e. artificial polypeptides, are capable of presenting a randomized peptide as a conformationally-restricted domain. Generally such presentation structures comprise a first portion joined to the N-terminal end of the randomized peptide, and a second portion joined to the C-terminal end of the peptide; that is, the peptide is inserted into the presentation structure, although variations may be made, as outlined below.

To increase the functional isolation of the randomized expression product, the presentation structures are selected or designed to have minimal biologically activity when expressed in the target cell.

The bioactive peptide interacts with a target protein within the cell. It is this interaction that results in an altered phenotype. The binding interaction between peptide and target can be used as the basis for identifying the target. For example, as outlined in the specification, if the target molecules are proteins, the use of epitope tags or purification sequences can allow the purification of primary target molecules via biochemical means. Alternatively, the peptide, when expressed in bacteria and purified, can be used as a probe against a bacterial cDNA expression library made from mRNA of the target cell type. Or, peptides can be used as "bait" in either yeast or mammalian two or three hybrid systems. Synthetically prepared labeled peptide can be used to screen a cDNA library expressed in bacteriophage for those cDNAs, which bind the peptide.

One of skill in the art would readily understand that the target molecule is not a part of the randomized nucleic acid, but is the "molecule with which the bioactive agent interacts". As recited in the claims, the target molecule is an intracellular molecule that binds to the bioactive peptide.

As set forth in the present claims, Applicants provide a method for screening peptides that, when expressed, alter the phenotype of a cell. The bioactive peptide is from 4 to 100 amino acids in length, and comprises a randomized portion. As described in the specification, the candidate nucleic acids which give rise to the candidate expression products are chemically synthesized, and thus may incorporate any nucleotide at any position. Thus, when the candidate nucleic acids are expressed to form peptides, any amino acid residue may be incorporated at any position. The synthetic process can be designed to generate randomized nucleic acids, to allow the formation of all or most of the possible combinations over the length of the nucleic acid, thus forming a library of randomized candidate nucleic acids.

The library may be fully randomized, with no sequence preferences or constants at any position. In a preferred embodiment, the library is biased. That is, some positions within the sequence are either held constant, or are selected from a limited number of possibilities. For example, in a preferred embodiment, the nucleotides or amino acid residues are randomized within a defined class, for example, of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, etc., or to purines, etc.

One of skill in the art would readily understand that the nucleic acid sequence encoding a candidate bioactive peptide will comprise sequences that is fully randomized, or where some positions are held constant or selected from a limited number of possibilities.

In certain of the claims, *i.e.* Claim 27 and claims dependent therefrom, the candidate bioactive peptide is joined at its N and C terminus to a presentation structure. Further, as set forth in Claim 27, the target molecule is identified by isolating the bioactive peptide, and binding the bioactive peptide to an intracellular target, and using that binding interaction to identify the target.

Applicants respectfully submit that Claim 28 is a proper dependent claim. The test as to whether a claim is a proper dependent claim is that it shall include every limitation of the claim from which it depends, or in other words that it shall not conceivably be infringed by anything which would not also infringe the basic claim.

As set forth in the MPEP, "a dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends. The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope."

The Office Action states that Claim 26 is unclear whether the nucleic acid binds with the target or the nucleic acid is expressed and then contacts the target. Applicants respectfully submit that the language of claims 26 and 27 are clear. The target is specified as an intracellular molecule that binds to the bioactive peptide, which peptide is encoded by the nucleic acid.

In view of the aboive amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112. Withdrawal of the rejections is requested.

Claims 26-38 are provisionally rejected under 35 U.S.C. 101 for statutory double patenting over claims 1 and 8-13 of published application 2002/0146710. Applicants respectfully submit that the present application claims an invention distinct from that of the '710 application. The present claims of the '710 application read as follows:

23. A method for *in vitro* screening for a cell whose phenotype is altered by expression of a transdominant intracellular bioactive peptide, said method comprising the steps:

a) introducing a molecular library comprising at least 10^4 different retroviral nucleic acid sequences, into a plurality of cells, wherein said retroviral nucleic acid sequences comprise an insertion of a nucleic acid sequence encoding a candidate bioactive peptide of from 4 to 100 amino acids in

length, wherein said candidate bioactive peptide comprises a randomized portion biased to minimize stop codons, and wherein said retroviral nucleic acid sequences are expressed in said cells to produce a plurality of randomized peptides;

b) screening said plurality of cells to detect a cell exhibiting an altered phenotype due to the expression of a transdominant bioactive peptide.

It may be noted that this claim does not recite the identification of a target sequence, and therefore does not meet the limitations of the present claims. Withdrawal of the rejection is requested.

Claims 26-28 and 30-31 have been rejected under 35 U.S.C. 102(e) as being anticipated by Jensen *et al.* (2001/0053523). Applicants have submited that Jensen *et al.* is not available as prior art to the present application. The PCT filing date for Jensen *et al.* is May 31, 1996. As quoted in the Office Action, 35 U.S.C. 102(e) provides for an application filed under the treaty defined in section 351(a) to be a reference. Priority documents filed under national law outside of the United States do not meet this requirement. Therefore, the earliest date on which Jensen can be available as a reference is the PCT filing date; i.e. May 31, 1996.

The present application claims priority to USSN 08/589,911, which was filed on January 23, 1996. The Examiner states that the present application is not entitled to the priority date, as the inventive entity is different from that of the parent application. Without conceding to the correctness of this assertion, Applicants agree to provide a Declaration from Dr. Garry Nolan unequivocably asserting that any subject matter described in the priority application and later claimed in the present application was solely conceived and invented by himself.

Withdrawal of the rejection is requested.

Claims 23-28 have been rejected under 35 U.S.C. 103(a) as unpatentable over Jensen in view of either Luzzago or Dower *et al.* As discussed above, Jensen *et al.* is not available as a reference. The secondary references do not make obvious the presently claimed invention.

Luzzago *et al.* describes a library of peptides inserted into the N-terminal region of a bacteriophage coat protein, with two cysteine residues flanking the insert. The Luzzago *et al.* library was not screened for an intracellular effect, but was selected for binding to antibodies. The present claims are distinguished from the prior art by screening for intracellular transdominant activity.

Dower *et al.* similarly utilizes a library of peptides attached to a bacteriophage structural protein, which peptides are screened for binding to an extracellular receptor. The present claims are distinguished from the prior art by screening for intracellular transdominant activity.

Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 103. Withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RIGL-004CON4.

Respectfully submitted,
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Date: Nov. 17, 2003

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